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A comparative assessment of chewing gum and ibuprofen in the management of orthodontic pain with fixed appliances; a multi-center randomised controlled trial

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Abstract

Introduction: The aim of this randomised trial was to investigate the effect of the use of a sugar free chewing gum vs. ibuprofen on reported pain and on bracket debonds, following the fitting of upper and lower fixed appliances.

Methods: Patients about to undergo orthodontic treatment using upper and lower fixed appliances were recruited into this 2-arm parallel design RCT in 9 trial sites in the South West of England. They were randomly allocated to one of two groups, namely the experimental chewing gum group or control ibuprofen group. Eligibility criteria included patients undergoing upper and lower fixed appliance therapy, aged 11-17 years, who were able to use ibuprofen and chewing gum. The primary outcome measure was pain experienced using a mean of three recordings on a scale of 0-10. Secondary outcome measures were pain experienced in the subsequent three days, again after the first archwire change, the use of ibuprofen and appliance breakages. Pain scores were recorded using a questionnaire and posted to a collection centre by the patient. Randomisation was by means of a central telephone service and comprised computer-generated pseudo-random numbers used to generate a sequential allocation list, with permuted blocks of variable size (two and four) and stratified by centre. Neither clinicians nor the patients were blinded to the intervention. Patients in the control group were only permitted to use ibuprofen whilst patients in the experimental group were allowed to use ibuprofen only if they didn't get sufficient analgesia from using chewing gum.

Data were analysed using the principle of Intention to Treat with multilevel modelling to reflect the structured nature of the data (scores within patient within site).

Results: 1000 patients were recruited and randomised in a ratio of 1:1 to either the chewing gum or ibuprofen (control) groups. The male to female ratio was similar in both groups

(chewing gum 35.6%: 64.4%, ibuprofen 38.4%: 61.6%). The pain questionnaire response rates were good at approximately 84% and 83% following appliance placement (chewing gum group 419: ibuprofen group 407) and 70% and 71% following the first archwire change (chewing gum group 343: ibuprofen group 341). The primary outcome was similar for the two groups: mean pain 4.31 in the experimental (chewing gum) group and 4.17 in the control (ibuprofen) group, difference 0.14 (95% confidence interval -0.13 to 0.41). There was a suggestion that the *relative* pain scores for the two groups changed over time, with the chewing gum group experiencing slightly more pain on the day of bond-up and less on the subsequent three days; however, the differences were not of clinical importance. There were no significant differences for the period following archwire change. The reported use of ibuprofen was less in the chewing gum group than in the control ibuprofen group: following appliance placement the mean number of occasions ibuprofen was used was 2.1 in the chewing gum group and 3.0 in the ibuprofen group (adjusted difference -0.96 (95%CI -0.75 to -1.17, p<0.001)); following archwire change the analogous figures were 0.8 and 1.5 occasions (difference -0.65 (-0.44 to -0.86, p<0.001)). Following both appliance placement and the first archwire change there was no clinically or statistically significant difference in the number of appliance breakages between the experimental chewing gum and control ibuprofen groups either following bond up (7% and 8.8%) or first archwire change (4.2% and 5.5%). No adverse events reported.

Conclusions: The use of a sugar free chewing gum may reduce the level of ibuprofen usage but has no clinically or statistically significant effect on bond failures

Registration: ISRCTN (79884739) and NIHR (6631) portfolios

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Introduction

It is well recognised that one of the most frequent side effects of orthodontic treatment involving fixed or removable appliances is pain as a result of tooth movement[1]. Pain has been reported to affect between 70% and 95% of children undergoing treatment and its intensity and duration varies from patient to patient, typically beginning 2 to 3 hours after appliance fitting[2,3,4,5,6] and lasting for up to 7 days, with a maximum intensity at 2 days[7,8,9]. Throughout an average 18 to 24 month course of orthodontic treatment experience of pain is not a one off event, and may be reported after each adjustment appointment, particularly if an arch wire is changed during fixed appliance therapy. For the majority of individuals this pain affects eating and for some it may also affect sleep[10,11]. Pain experienced as a result of orthodontic treatment has been cited as a major barrier to treatment acceptance and the principal reason for its discontinuation, which in one study was found to be as high as 8%[12]. This has economic implications not only for the patient and their family, but also for any publicly funded Health Service.

Why orthodontic pain occurs is still unknown, but it has been described in a review by Krishnan (2007)[13] as possibly arising as a result of the pressure, ischaemia and inflammation induced within the periodontal ligament during the induced tooth movement. This then leads to changes in blood flow, the release of mediators such as prostaglandins and a resultant hyperalgesia. This is likely to be very much an oversimplification, as the neural pathways involved in pain are complex and are also known to be intimately related to emotional state including fear, anxiety and mood[14].

Analgesics such as ibuprofen or paracetamol are often used to alleviate orthodontic pain. Sometimes they are taken pre-emptively, prior to a fitting or adjustment appointment, but

more often are taken as the teeth become painful following such an appointment. Both drugs, although effective in reducing pain, can cause adverse reactions[15, 16]. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) whose analgesic action is thought to occur peripherally through its ability to inhibit the synthesis of prostaglandins at a site of tissue injury. It has been suggested that prostaglandin inhibition may result in a slowing of orthodontic tooth movement, leading some to question whether orthodontic patients should use NSAIDs for pain relief as it could prolong their treatment[17]. However, at present the clinical significance of NSAIDs on orthodontic tooth movement is unclear, particularly if analgesics are only taken for a short period of time, at the beginning and at intervals throughout a course of treatment.

To date, largely anecdotal evidence has suggested that the use of chewing gum may provide some pain relief and either eliminate or reduce the need for other forms of analgesia. However, the effectiveness of use of chewing gum use has not been widely investigated, probably because of fear that gum chewing increases the frequency of appliance breakages. A small randomised controlled trial (57 patients aged 11-18 years) looking at the effect of chewing gum on the impact of fixed appliance therapy, including its effect on pain[18], suggested that chewing gum not only lessens the impact, but also reduces the level of pain experienced. In this study, both the gum and no gum groups were permitted to take analgesics if required. However, how much and what analgesics were taken was not recorded, merely whether or not any was taken. Although it was reported that there was no statistically significant difference in whether or not analgesia was used by the two groups, it is not possible to determine whether or not the effect of chewing gum for pain relief was additive or whether one group took more analgesics than the other.

Specific objectives and hypotheses

1000, 11-17 year old patients undergoing a course of upper and lower fixed appliance therapy were recruited in order to investigate the effect of the use of a sugar free chewing gum on reported pain following the fitting of full upper and lower fixed appliances. The secondary outcome measures were pain experienced in the subsequent three days, pain experienced after the first archwire change, the use of chewing gum or ibuprofen at each time period and number of appliance breakages. .

Materials and Methods

Trial design and any changes after trial commencement

The investigation comprised a prospective 2-arm parallel design multicentre randomised controlled trial in nine hospital orthodontic departments in the South West of England with a 1:1 allocation ratio. Ethics Committee (08/H0106/139), R&D and MHRA (Eudract 2008-005522-36) approvals were obtained and the trial was registered on the ISRCTN (79884739) and NIHR (6631) portfolios. The primary outcome measure was pain experienced on the day of appliance placement. Secondary outcome measures were pain experienced in the subsequent three days, pain experienced after the first archwire change, the use of chewing gum or ibuprofen at each time period, and number of appliance breakages.

There were no changes to the trial following commencement.

Participants, eligibility criteria and settings

1000 consecutive patients aged between 11 and 17 years, who about to have upper and lower fixed appliances fitted were recruited into the study. As this was pragmatic clinical-

effectiveness trial to determine whether chewing gum might be a reasonable "substitute" for ibuprofen, it was designed to reflect the real-world across nine trial centres. There was therefore no stipulation as to the type of fixed appliance, aligning wires, ligation method, type of malocclusion, number of teeth to be extracted or not prior to commencement, or the seniority of the orthodontist recruiting and treating the patients. There were however specific exclusion criteria, namely for patients with a history of:

- Hypersensitivity to ibuprofen or any of the other ingredients
- Hypersensitivity reactions to aspirin or other NSAIDs including asthma, rhinitis or utricaria
- Current or previous peptic ulceration or bleeding of the stomach
- Severe heart failure

Patient information leaflets explaining the proposed study were given to patients and their parents, following which they were invited to complete a written consent form.

Interventions

Immediately after the fitting of the appliances each patient was then randomly allocated to either the experimental (chewing gum) or the control group (ibuprofen).

Experimental group (chewing gum)

Once recruited, patients within the intervention group were provided with sugar free chewing gum (Orbit Sugar Free Gum, Wrigley, Thame, UK) and ibuprofen tablets (250mg Tablets, Wockhardt UK Ltd, Wrexham, UK). They were instructed to use the chewing gum for pain relief if required following the fitting of their upper and lower fixed appliances, but were also instructed that they could take ibuprofen for pain relief if the chewing gum was not effective. Information on maximum dosage and frequency of use were provided. The

patients were also provided with a pain questionnaire to complete, detailing their pain experience and what they took to deal with the pain over the three days following appliance placement. The pain questionnaire comprised a series of identical numerical pain rating scales. Each rating scale contained 11 points and ranged from no pain (0) to worst pain imaginable (10). Patients were instructed to record the degree of discomfort when biting and chewing at 2 hours after appliance placement, 6 hours after placement, at bedtime on the day of the appointment, at bedtime the next day, at bedtime 2 days after the appointment, and at bedtime 3 days after the appointment, following the protocol of Bradley *et al.* (2007)[19]. If the 6 hour reading coincided with bedtime only one reading was used. They were also asked to record in the log at each time period what was taken and when, during the first 3 days after appliance placement.

Control group

Patients within the control group were provided with ibuprofen (250mg Tablets, Wockhardt UK Ltd, Wrexham, UK) and were instructed to use it for pain relief if required following the fitting of their upper and lower fixed appliances. As per normal practise patients were advised not to chew gum whilst wearing their fixed appliances. Information on maximum dosage and frequency of ibuprofen use were again provided and as in the intervention group, the patients were asked to complete the pain questionnaire detailing their pain experience and what they took to deal with the pain over the three days following appliance placement.

Follow up appointment, first archwire change

At the next routine adjustment appointment at which the archwires were changed, the patients were provided with the same analgesia regimen (intervention group – chewing gum

and ibuprofen; control group – ibuprofen) and instructions as previously allocated and once again asked to complete another pain questionnaire on their experiences and usage over the following 3 days. In all cases the patients were provided with reply paid envelopes for the pain questionnaires to be returned to the co-ordinating centre for the trial.

At each of the two appointments following the fitting of the appliances the presence or absence of appliance breakages was also recorded. At this point the treating orthodontist would be blinded to the group allocation.

Sample size calculation

The primary outcome measure was the mean pain experienced following appliance placement/adjustment. The results of a much smaller study, which utilised a continuous visual analogue scale (VAS) were initially used to perform a sample size calculation assuming a standard deviation of 20mm on a 100mm VAS pain scale[19]. This indicated that complete data on 394 patients per trial arm would give an 80% power to detect a difference of 4mm in the mean of the readings, when using a two-tailed t-test. Allowing for 20% loss to follow-up required 493 per trial arm; we therefore aimed to recruit and randomise a total of 1000 patients. However, with 6 time intervals for each intervention period (appliance placement and then initial archwire change) this would require the reproduction and measurement of 14,000 10cm VAS lines. It was therefore decided to record pain experience using a categorical scale from 0 “no pain” to 10 “worst pain imaginable” at 2 hours, 6 hours and bedtime up to 3 days. Not only would a categorical scale rather than a continuous VAS aid data collection and database entry, but would also reduce the chances of bias in the reproduction of the scale on photocopying and subsequent measurement[20].

Randomisation

The randomisation strategy comprised computer-generated pseudo-random numbers used to generate a sequential allocation list, using permuted blocks of variable size (two and four) and stratified by centre. This list was generated by the Research Design Service Co-ordinating Centre in Taunton and remained secure from the recruiting clinicians. Allocation to a trial arm was determined by central telephone randomisation once a patient was recruited.

Blinding

Neither the clinicians nor the patients were blinded to the intervention. However the person performing the data entry and the statistician were blinded to the intervention.

Statistical Analysis

All statistical analyses were conducted on the basis of the intention-to-treat principle as far as possible. For the primary outcome of pain over the day of bond-up, characteristics of patients with missing data was considered. Age was weakly predictive of missingness, while gender was not predictive. Multiple imputation of the missing data using age and treatment group was performed and results were very similar to those obtained by using complete cases only; for simplicity only the latter results are presented. The primary outcome was compared between groups using mixed effects linear regression, with treatment group as a fixed effect and centre as a random effect.

Further analyses of pain scores were conducted using multi-level modelling. Measures were taken at six time points after bond-up and similarly six time points after archwire change. Mixed effects regression models included treatment group, visit (bond up or archwire

change) and time point as fixed factor effects (with inclusion of interactions as necessary), with centre as a random effect and individual (nested within centre) also as a random effect. Within this structure, a linear mixed effects model was fitted for pain scores and the number of times ibuprofen was used, while a logistic mixed effects model was used for whether ibuprofen was used at all.

The data were analysed using Stata version 14.0 (StataCorp, USA)

Results

Participant flow

1000 patients aged 11-17 years were randomised in a 1:1 ratio to either the experimental chewing gum or the control ibuprofen group. 499 received chewing gum, of which 419 pain questionnaires were analysed following the initial bond up and wire placement and 343 questionnaires were analysed following the first arch wire change. There were 491 patients in the control group of which 407 pain questionnaires were analysed following the initial bond up and wire placement and 341 questionnaires were analysed following the first arch wire change. The CONSORT diagram detailing the patient flow through the study is illustrated in Figure 1. Recruitment began in December 2009, was completed in May 2012 and the final pain questionnaire was received following the final recruit's first archwire change in September 2012.

Baseline Data

The baseline characteristics for gender, age and recruitment site in both the chewing gum and ibuprofen groups were similar and are illustrated in Table 1.

Pain

For the primary outcome, the mean pain (and standard deviation SD) reported on the day of bond-up was 4.31 (SD 2.01; n=418) in the intervention (chewing gum) group and 4.17 (SD 1.97; n=407) in the control (ibuprofen only) group. The adjusted mean difference was 0.14 (95% confidence interval -0.13 to 0.41), p=0.32.

Figure 2 illustrates mean reported pain at each time point in the two groups (figure 2a following bond-up and figure 2b following archwire change). When a multilevel model was fitted for reported pain with fixed effects for treatment group, visit (bond-up or archwire change) and time point (1-6) (and random effects for patient nested within site), significant interactions were found for visit x time point ($p<0.001$) and treatment group x time point ($p=0.03$). Separate models were therefore run for each visit separately. For bond-up, a model without any interaction for treatment group x time point suggests there is no difference between groups, with the overall mean pain difference (intervention – control) estimated as -0.03 (95% confidence interval -0.27 to 0.20, p=0.78). However, when an interaction term is included for treatment group x time point, it is statistically significant ($p=0.006$). As confirmed visually by figure 2a, pain scores are slightly higher in the chewing gum group on the day of bond-up, but lower in the subsequent three days. None of these individual time points achieve statistical significance, and arguably are not of clinical relevance, the difference between groups never greater than 0.3. For the archwire change visit, the interaction term was not significant (p=0.56) and neither was treatment group as a main effect (difference = -0.04, 95%CI -0.32 to 0.24, p=0.78).

Ibuprofen use

The protocol allowed patients in the intervention (chewing gum) group to take ibuprofen if they felt pain relief following chewing gum use was insufficient. Ibuprofen use was recorded on the day itself (2h, 6h, bedtime) and for each of the subsequent three days, for each visit. Figure 3 shows the percentage of patients reporting use of ibuprofen at the various time points following bond-up (figure 3a) and archwire change (figure 3b). Overall 82% of patients in the chewing gum group and 91% in the control group took ibuprofen following bond-up; the overall mean number of times ibuprofen was taken was 2.1 and 3.0 respectively. Following archwire change the analogous figures were 42% (mean 0.8 occasions) and 60% (1.5 occasions). Multilevel models again reported significant interactions for visit x time point indicating the logic in looking at each visit separately. At bond-up, the interaction term treatment group x time point was weakly significant ($p=0.044$), suggesting some slight differences in the relative use of ibuprofen between groups across the time points, but with no obvious trend across time (figure 3a). With or without the interaction term, the main effect for treatment group was highly statistically significant; for ease of interpretation, dropping the interaction term gives an odds ratio of 0.46 (95%CI 0.40 to 0.53, $p<0.001$) for the use of ibuprofen in the chewing gum group relative to the control group. After archwire change, no treatment x time point interaction was evident ($p=0.76$), and ibuprofen use was again lower in the chewing gum group: odds ratio = 0.29, 95% CI 0.17 to 0.51, $p<0.001$ (figure 3b). The centre-adjusted mean difference in the number of occasions ibuprofen was taken was -0.96 (-0.75 to -1.17, $p<0.001$) following bond-up and -0.65 (-0.44 to -0.86, $p<0.001$) after archwire change.

Bracket Debonds

Another important secondary outcome measure was the number of appliance breakages between the experimental chewing gum and control ibuprofen groups. There was no clinically or statistically significant difference between the two groups either following bond up (7% and 8.8%) or first archwire change (4.2% and 5.5%) (Table 2).

Harms

There were no other reported adverse events.

Discussion

In this randomised controlled trial investigating the use of chewing gum for the relief of orthodontic pain, the results suggest there was no clinically important difference in reported pain between the intervention group, who used chewing gum as the principal method of pain relief, and the control group who were only permitted to take ibuprofen to relieve their orthodontic pain. There is a suggestion that those using chewing gum experience slightly more pain on the day of bond-up itself but slightly less in the following three days. This alone does not give much of an indication as to whether chewing gum is effective for pain relief, as the protocol permitted the use of ibuprofen in both groups where necessary. However, when looking at the use of the latter in both groups there would appear to be a clinically and statistically significant effect, with those patients in the chewing gum group reporting less use of ibuprofen for pain relief following appliance placement and first archwire change than those in the control group. The results would also suggest that in the experimental chewing gum group over 80% of patients used chewing gum on the day of appliance placement and over 50% used it sometime over the subsequent 3 days. Despite

this high level of chewing gum use there was no clinically or statistically significant difference in appliance breakages as measured by recorded bond failures.

Unlike the small study by Benson *et al*. (2012)[18], which principally focussed on the effect of chewing gum on the impact of orthodontic appliance therapy and where at 1 week almost twice as many patients in the chewing gum group used painkillers compared to the control group, we found no important difference in the levels of reported pain between the chewing gum and control (ibuprofen) groups. What was significant though was that those patients who used chewing gum in our study used less ibuprofen. This is also in contrast to another small study by Farzanegan *et al*. (2012)[21] on just 50 female patients, who recommended that chewing gum or bite wafers could be used as a substitute for ibuprofen in the relief of orthodontic pain. This recommendation is certainly not supported by the findings of the current investigation.

The major strengths of the current investigation into the use of chewing gum for the management of orthodontic pain were the sample size, which was large (n=1000), and the fact that it was a multicentre randomised controlled clinical trial. The results are therefore generalisable. The major weakness was the requirement for the patients to complete a self-reported pain questionnaire and to post this back on completion. Despite this limitation, the response rates were good at almost 84% and 83% (chewing gum group: ibuprofen group) following appliance placement and 70% and 71% (chewing gum group: ibuprofen group) following the first archwire change (Figure 1). The drop-out rates were lower than what was allowed for in the power calculation for the primary outcome; however, following archwire change the drop out was slightly higher and consequently there was slightly less power for this aspect.

Conclusions

The results of this randomised controlled trial would indicate:

1. The use of a sugar free chewing gum following initial orthodontic fixed appliance placement, and at the subsequent archwire change, may reduce the level of ibuprofen usage.
2. The use of chewing gum for pain relief had no clinically or statistically significant effect on bond failures

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Figure Captions

Figure 1 CONSORT flow diagram

Figure 2 Mean pain scores after (a) bond-up and (b) archwire change. Error bars represent +/- 1SE. “Bedtime” is positioned on the time axis according to the average time reported.

Figure 3 Percentage using Ibuprofen after (a) bond-up and (b) archwire change. Error bars represent +/- 1SE. “Bedtime” is positioned on the time axis according to the average time reported.

Table Captions

Table 1 Baseline characteristics of the patient sample

Table 2 Number of patients experiencing an appliance breakage from appliance placement to first archwire change and from first archwire change to second archwire change.